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09/676,436	09/29/2000	Donna T. Ward	RTS-0169	5700

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EXAMINER

LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/676,436	WARD ET AL.
Examiner Karen Lacourciere	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM

THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed

- after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on ____.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,2 and 4-20 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
 5) Claim(s) ____ is/are allowed.
 6) Claim(s) 1,2 and 4-20 is/are rejected.
 7) Claim(s) ____ is/are objected to.
 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. ____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.

4) Interview Summary (PTO-413) Paper No(s) ____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: ____.

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DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,2, 4-10 and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites an antisense compound that "specifically hybridizes with", but does not indicate what the antisense compound hybridizes with. It is unclear, for example, if the antisense hybridizes with the nucleic acid encoding MEKK4 (SEQ ID NO:3), the protein product of a nucleic acid encoding MEKK4 or another cellular component, for example, another nucleic acid. Claims 2, 4-10 and 12-20 are indefinite for the same reasons, due to their dependence on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* (cell culture) inhibition of MEKK4, does not reasonably provide enablement for *in vivo* (whole organism) methods of treatment using antisense targeted to MEKK4. The specification does not enable any person skilled in

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the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 15-20 are drawn broadly to inhibition of the expression of MEKK4 in any cell *in vivo* (whole organism) for the treatment of any disease that is associated with MEKK4. Claims 17-20 are further drawn to treating any immunologic, inflammatory or hyperproliferative disorder, including cancer, using antisense targeted to a nucleic acid encoding MEKK4.

The specification provides examples wherein chimeric phosphorothioate antisense targeted to a nucleic acid encoding MEKK4 inhibited the expression MEKK4 *in vitro* (cell culture) in human cell lines. The specification does not demonstrate any correlation with the inhibition of MEKK4 in cells in culture and a treatment effect for any disease or condition associated with MEKK4. The specification does not present any examples wherein antisense targeted to MEKK4 was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to MEKK4 inhibited the expression of MEKK4 in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition,

including an immunologic, inflammatory or hyperproliferative disorder, including cancer, using antisense targeted to MEKK4.

The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to MEKK4, including specific immunologic, inflammatory or hyperproliferative disorders or specific types of cancer, and what cells to target for a particular disease or condition.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of MEKK4 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological

activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to MEKK4 to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the inhibition of the expression of MEKK4, what specific cells to target with MEKK4 antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of MEKK4 to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic

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application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 15-20 over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takekawa et al. (reference AC on PTO form 1449, filed 09-29-2000 and Genbank Accession Number AF002715) in view of Johnson (US Patent No. 5,981,265, referred to herein as '265, cited on PTO form 1449, filed 09-29-2000), Johnson (US Patent No. 6,312,934, referred to herein as '934), Johnson (US Patent No. 6,333,170, referred to herein as '170), Milner et al. (Nature Biotechnology, Vol. 15, pages 537-541, 1997) and Baracchini et al. (US Patent No. 5,801,154)

Claims 1, 2 and 4-15 are drawn to compounds 8 to 50 nucleobases in length that specifically hybridize to a nucleic acid encoding MEKK4 (SEQ ID NO: 3) and inhibit the expression of MEKK4 or a compound which specifically hybridizes to at least an 8 nucleobase portion of an active site on a nucleic acid encoding MEKK4. Further limitations include wherein the antisense comprises modified bases, including 5-methylcytosine modifications; modified sugars, including 2'-O-methoxyethyl modifications; internucleoside linkage modifications, including phosphorothioate; chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of MEKK4 in cells *in vitro*.

Takekawa et al. teach the full length sequence of MTK1 (see page 4980, second column, fourth paragraph, and Genbank Accession number AF002715), which is the same sequence as SEQ ID NO: 3 of the instant application, and teach that MTK1 is a

human mitogen-activated protein kinase kinase kinase, and likely to be the human homologue of MEKK4 (see for example, page 4980, first column). Takekawa et al. do not teach antisense targeted to SEQ ID NO: 3 or inhibiting the expression of MTK1 (MEKK4) in cells using antisense, nor do they teach the modifications claimed.

'265, '934, and '170 each teach making antisense targeted to nucleic acids encoding MEKK proteins, including MEKK4, however, none of these patents teach SEQ ID NO: 3. '265 (see for example columns 15-16) teaches making antisense targeted to nucleic acids encoding MEKK proteins and provides examples of nucleic acids encoding mouse MEKK proteins, including mouse MEKK4. '934 teaches making antisense targeted to nucleic acids encoding MEKK proteins, particularly the human versions of MEKK proteins (see for example, columns 14-15) and teaches making modifications to that antisense, including base modifications and backbone modifications, such as phosphorothioate, and teaches a length for antisense in the range of 15 to 50 nucleotides long (see for example col. 14, lines 50-52 of '934). '170 teaches making antisense targeted to nucleic acids encoding MEKK proteins (see for example columns 27 to 29) and provides examples of nucleic acids encoding mouse MEKK proteins, including MEKK4 splice variants, and teach modifying antisense for nuclease stability, including phosphorothioate modifications (see for example column 28. '170 teaches that antisense targeted to nucleic acids encoding MEKK can be used to investigate the role of MEKK in disease states as well as the normal cellular function of MEKK in healthy tissue and can be used in this capacity in cell culture (see '170, column 28 line 63 to column 29, line2).

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Milner et al. teach methods of making and screening antisense molecules against a desired target gene in any region of the gene, including the 5' or 3' untranslated regions or the coding region.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and teach antisense oligonucleotides of 8-30 nucleotides in length (see for example columns 6-9). Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an antisense molecule targeted to a nucleic acid encoding MEKK4 (SEQ ID NO: 3), based on the sequence taught by Takekawa et al., because '265, '934, and '170 each teach making antisense targeted to nucleic acids encoding MEKK proteins, including MEKK4, and Takekawa et al. teach that their nucleic acid encodes the human homologue of MEKK4 and is involved in the same signaling pathway in humans as the proteins disclosed by '265, '934 and '170. Methods of making antisense targeted to a known gene were well known in the art at the time the instant invention was made, as exemplified by Milner et al. It further would have been obvious to make such antisense of a length within the range of 8-50 nucleobases (as taught by Baracchini et al. and '170), because antisense of a short length are more easily synthesized and easier to deliver to cells and '170 explicitly teaches antisense within this range (15-50 nucleotides) for targeting nucleic acids encoding MEKK

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proteins. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3) and because both '170 and '934 teach modifying antisense targeted to MEKK nucleic acids. It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al.

One of ordinary skill in the art would have been motivated to make antisense targeted to MEKK4 (SEQ ID NO: 3), because '265, '934 and '170 each teach targeting nucleic acids encoding MEKK proteins, including MEKK4 ('265 and '170) and human MEKK proteins ('934), using antisense and Takekawa et al. teaches that SEQ ID NO: 3 encodes a human MEKK4 homologue. Antisense was well known in the art as a means to selectively inhibit the expression of a gene and '170 and '934 particularly teach using antisense targeted to nucleic acids encoding MEKK proteins as a means to study the cellular function of MEKK proteins. Takekawa et al. teach that the role of MTK1 (SEQ ID NO:3) is not fully understood (see for example, discussion section) and one of ordinary

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skill in the art would have been motivated to make antisense to MEKK4 (SEQ ID NO: 3) to use *in vitro* in order to study the role of MTK1 (MEKK4, SEQ ID NO:3) in cells. One of ordinary skill in the art would have been motivated to make such antisense within the range of 8-50 nucleotides in length and with the modifications and in the compositions taught by Baracchini et al. for the benefits of ease of synthesis and delivery and to realize the benefits of improved stability and hybridization properties these modifications provided.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of MEKK4 (SEQ ID NO:3), because the sequence of a nucleic acid encoding MEKK4 (SEQ ID NO: 3) was known in the art and methods of screening for antisense to a known gene were routine (see for example Milner et al.).

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding MEKK4 in a method of inhibiting the expression of MEKK4 (SEQ ID NO: 3) in cells *in vitro* (cell culture), because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding MEKK4 (SEQ ID NO:3) and '170 and '934 both teach using antisense targeted to nucleic acids encoding MEKK proteins in cells in culture as a means to study cellular function.

Therefore, at the time the instant invention was made, the invention of claims 1, 2 and 4-15, as a whole, would have been obvious to one of ordinary skill in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen Lacourciere PATENT EXAMINER
Karen A. Lacourciere TC 1600
June 5, 2002